## REMARKS

In the Final Office Action of June 5, 2007, claims 76, 79-80, 82-84 and 93-97 were pending and were rejected. Claims 76, 79-80, 83, 84, and 93-94 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Claims 94-97 were separately rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Claims 95-97 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claims 76, 79-80, 82-84 and 93-97 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Xu et al., U.S. 2002/0072117 and U.S. Patent No. 6,642,048 B2. Claims 76 and 79-97 were further rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bodnar et al. (WO 99/20740) in view of Bongso et al. (*Hum. Reprod.* 9 (11): 2110-2117 (1994)). Additionally, the Examiner states that certified copies of the priority documents are missing from the file.

In response to the Final Action, claim 97 is canceled. New claims 101 and 102 are added. Claims 76, 80 and 82-84 have been amended as indicated above. All amendments and newly added claims are supported by the specification. See specification, page 16, lines 1-25 for reference to preparing fibroblast feeder layers using fetal and adult tissues. Also, see page 20, line 28 to page 21, line 11 for description of culturing fibroblast feeder layer. Claim 76 recites that the human fibroblast feeder cells are obtained from "a differentiated tissue". It is respectfully submitted that human embryonic, fetal and adult stages of development all inherently possess differentiated tissues. Therefore, the use of fetal and adult tissues such as muscle, skin and fallopian tube, disclosed in the specification, fully supports the recitation of "a differentiated tissue" in amended claim 76. No new matter is introduced by the amended and newly added claims.

The following remarks address the issues raised by Examiner.

Priority

Applicants will provide certified copies of the priority documents in due course.

Enablement

The Examiner rejects claims 76, 79-80, 83-84 and 93-94 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. The Examiner relies on Xu's statement that adult fibroblasts feeder cells generally do not support undifferentiated stem cell growth, therefore, one would not expect Applicants' claimed medium to be enabled for more than the human adult fallopian tube fibroblasts, which are specifically exemplified in the application.

Although not in agreement with Examiner's rationale, Applicants have amended the claims to delineate that fibroblast feeder cells are obtained from a differentiated human tissue (claim 76), such as skin, muscle, and fallopian tube (new claims 101-102). In this context, Applicants clarify the functional and biological connection between *adult* (i.e., newborn and older) fibroblasts (such as adult oviduct fibroblasts) and fetal tissue-derived fibroblasts. These fibroblasts share an important feature – they are all derived from a differentiated tissue, and thus, are themselves differentiated to the extent that they function as fibroblasts in these differentiated tissues. These fibroblasts are in contrast to the completely uncharacterized stem-cell derived "fibroblast-like" cells described by Xu et al.

It is further submitted that Examiner has not provided concrete evidence or reasoning, as is required, to support her conclusion that the claims are not enabled for the broad scope of human fibroblasts. MPEP 2164.04. Accordingly, the stated rationale for rejecting the claims is not sufficient to make out a *prima facie* case of nonenablement.

In contrast, Applicants respectfully submit that the claims, as presently amended, are fully supported by the specification. More specifically, the specification teaches the use of fibroblast cells that are fully differentiated fibroblasts, derived from tissue consistent with the fibroblast type. For instance, in addition to HFAT cells derived from human fallopian tube, the specification teaches that HAM fibroblasts are derived from muscle tissue, and HAS fibroblasts are derived from human skin.

The Examiner's attention is directed to page 36 of the specification, where preparation of a defined human fetal layer is described. Although fetal muscle is illustrated, the tissue is muscle from which fully defined and differentiated cells (fibroblasts) are derived. The conditioned media obtained from fetal muscle is as effective as the conditioned media obtained from HAFT fibroblasts which are also fully differentiated.

The use of HAS fibroblasts are also disclosed on pages 33 and 34 of the specification, where fibroblasts specifically were prepared from the fetal skin fibroblast. Again, the fetal skin fibroblasts were equally capable of prolonging culture of the hES cells of the undifferentiated state as were the HAFT cells.

Even though these examples in the specification illustrate the use of fetal derived fibroblasts, however, because fetal and adult tissues both contain fully differentiated fibroblasts, it is respectfully submitted that the results achieved with the fetal derived (fully differentiated) fibroblasts can be reasonaly extropolated to adult fibroblasts.

Therefore, Applicants respectfully submit that based on the specification, those skilled in the art would be able to practice the claimed methods using fibroblasts obtained from a differentiated tissue, such as muscle, skin and fallopian tube, as presently claimed,

without undue experimentation. Withdrawal of the enablement rejection of claims 76, 79-80, 83-84 and 93-94 is respectfully requested.

Claims 94-97 are separately rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Specifically, the Examiner indicates that the cells referenced in claims 95-96 are fetal cells, and the cells referenced in claim 97 are embryonic cells. The Examiner alleges that the specification does not provide enablement for using these fetal and embryonic cells in the claimed methods.

Claim 97 has been canceled by the foregoing amendment, rendering the rejection thereof moot. As to claim 94, it is unclear to Applicants why this claim is included in the rejection. With respect to claims 95-96, Applicants respectfully direct the Examiner's attention to the specification on pages 33-34 and 36, where the use of fetal skin fibroblasts and fetal muscle fibroblast cells are specifically demonstrated, as discussed above. As such, the enablement rejection of claims 94-97 is overcome. Withdrawal of the rejection is therefore respectfully requested.

Indefiniteness

Claims 95-97 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner indicates that these claims depend from claim 76, which requires adult fibroblast feeder cells. On the other hand, claims 95-97 reference cell lines that are of a fetal or embryonic origin.

Claim 97 has been canceled. Claim 76, as presently amended, refers to fibroblast cells obtained from a differentiated tissue. The fetal cells referenced in claims 95-96 are obtained from a differentiated tissue (i.e., muscle and skin tissues of a fetus). Therefore, it is

respectfully submitted that claims 95-96 are not indefinite. Withdrawal of the rejection is therefore respectfully requested.

Anticipation- §102(e)

Claims 76, 79-80, 82-84 and 93-97 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Xu et al. (U.S. 2002/0072117 A1). Claims 76, 79-80, 82-84 and 93-97 are also rejected under 35 U.S.C. §102(e) as allegedly anticipated by Xu et al. (U.S. Patent No. 6,642,048 B2).

The Examiner argues that the conditioned medium presently claimed is not, or has not been shown to be, patentably distinct from the conditioned medium produced by the "fibroblast like cells" of Xu et al. The Examiner asserts that the instant claims are product-by-process claims, and therefore, a prior art product (e.g., the conditioned medium of Xu et al.) may anticipate the claimed medium even if made by a distinct process. Final Office Action, page 8.

In the first instance, Applicants respectfully disagree that the disclosures of Xu et al. are sufficient to shift the burden to Applicants under §102(e) to prove there are distinctions between the conditioned media of Xu et al. and the claimed conditioned media. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)." MPEP 2131. It is respectfully submitted that neither of the Xu et al. references expressly or inherently describe each claim limitation, and therefore, do not anticipate the claims. Specifically, the references provide absolutely no disclosure relating to the use of human feeder cells obtained from differentiated tissues. Thus, there is no basis to conclude that the

disclosures of Xu et al. are sufficient to make out a *prima facie* case of anticipation in the first instance.

In addition, "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (Emphasis added). In this connection, Applicants respectfully submit that the human feeder cells disclosed by Xu et al. are not true fibroblasts from a differentiated tissue, which are employed to produce the presently claimed conditioned medium. Therefore, it does not necessarily follow that the conditioned media of Xu et al. is patentably indistinct from the condition media produced by Applicants' differentiated fibroblasts.

The human feeder cells ("hEF") are referred to throughout Xu et al. as "fibroblast-like" (e.g., see paragraph 0026-27 in the '117 application), or as having the characteristics of a fibroblast or muscle cell lines (the '048 patent, col. 3, line 13), or as mesenchymal cells (see the '117 application, abstract and paragraph 0018). Mesenchymal cells are undifferentiated cells that may differentiate into bone, cartilage, connective tissue, blood, endothelial cells or smooth muscle. This key distinction between the "hEFs" and mEFs, disclosed by Xu et al., is apparent by the consistent reference by Xu et al. to mEF cells only as fibroblasts (e.g., see the '117 application, paragraphs 0024 and 0141). Therefore, Xu et al. themselves acknowledge the difference between true fibroblasts and the undefined fibroblast-like or muscle cell-like feeder cells. Further, Xu et al. obtained the hEFs by differentiating human ES cells and removing the elongated cells that are arbitrarily referred to as fibroblast-like. It is respectfully submitted that the ordinary skilled artisan would also acknowledge the

differences between the human feeder cells, and the true human fibroblasts described and claimed in the subject application, and would not consider the human feeder cells of Xu et al. to be defined human fibroblasts.

Furthermore, the fibroblasts from which the conditioned media is developed in the present application do not require genetic modification with TERT (telomere reverse transcriptase). In contrast, in Xu et al., the fibroblast-like cells require genetic modification with TERT in order to maintain the cells in a premature state. The Examiner's attention is directed to column 5, lines 28 to 35 of the '048 patent where the specification states that:

> "... fibroblasts derived from adults are generally not used as feeder cells suggesting that more mature cells lose the ability to provide the factors requisite to support stem cell growth. It has now been discovered (by Xu et al) that feeder cells can be immortalised and maintained in long term culture without causing them to lose the ability to produce high quality conditioned medium. For example primary mouse embryonic fibroblasts can be immortalised by genetically altering them to express telomerase reverse transcriptase".

The passage goes on to state that these cells can be perpetuated in culture providing a ready source of high quality medium. The fibroblast-like cells taught by Xu et al. are derived from differentiating embryonic stem cells and are in a premature state. Based on the cited passage in Xu et al., it would be understood that older (i.e., mature and differentiated) cells do not produce the same products, and therefore it is necessary to maintain the hES derived feeders in a premature state. Xu et al. therefore provide a conditioned medium from a particular cell type which is a premature cell type and which has been genetically modified to ensure that it remains in this premature state so that high quality conditioned media will be produced. In

contrast, the fibroblasts recited in the present claims are fully matured fibroblasts derived from a differentiated tissue.

Moreover, the conditioned media developed in the current application can derive from a low passage of the fibroblast feeders obtained from muscle, skin or fallopian tubal tissue. A passage number of only 6 passages in needed (Example 1(a) in the specification). There is no requirement to immortalize the cells. Xu et al. on the other hand, found it necessary to immortalize the cells with TERT before conditioned media was developed.

All these differences in the feeder cells from which a conditioned medium is prepared support Applicants' position that it does not necessarily follow that the conditioned media of Xu et al. is patentably indistinct from the condition media presently claimed. Further support for Applicants' position is found in apparent distinctions between the presently claimed conditioned medium and the conditioned medium of Xu et al. themselves.

Specifically, Xu et al. discloses that LIF alone is ineffective in maintaining the hES cells in an undifferentiated state in the absence of a feeder layer. See the '048 patent, col. 28, lines 19-24. In contrast, Applicants' medium effectively maintains hES cells in the undifferentiated state in the absence of LIF. See the present specification, pages 17, 22 and 24. In other words, it appears that the conditioned media of Xu et al. also requires LIF to be effective, whereas the claimed conditioned medium does not require LIF.

Similarly, the conditioned medium of Xu et al. requires basic fibroblast growth factor (bFGF) in order to maintain cultures of hES cells in the undifferentiated state. In the absence of bFGF, the cells displayed a differentiated morphology, as taught by Xu et al. See the '048 patent, col. 27, lines 50-67. This is not the case with Applicants' conditioned

medium. See the preparation of a conditioned medium in Example 1 of the specification, where HES medium was used and no rhbFGF was added.

In conclusion, the conditioned medium of Xu et al. is produced by an undefined cell type, and requires LIF and, bFGF or hbFGF for effectiveness. In contrast, Applicants' conditioned medium is prepared with fibroblasts obtained from differentiated tissues. Further, Applicants' conditioned medium does not require LIF or bFGF. It is respectfully submitted that these differences clearly indicate that the allegedly inherent characteristics of Applicants' conditioned medium are not present in the conditioned media taught by Xu et al. Accordingly, withdrawal of the rejections under §102(e) is respectfully requested.

Obviousness

Claims 76 and 79-97 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bodnar et al. (WO 99/20740, "Bodnar") in view of Bongso et al. (*Hum. Reprod.* 9 (11): 2110-2117 (1994), "Bongso").

The Examiner states that Bodnar teaches the growth of primate-derived primordial stem cells from primates and humans by culturing the cells in a nutrient medium, and a substrate consisting of feeder cells and an extracellular matrix component. The Examiner alleges that Bodnar also teaches making a conditioned medium by supplementing with soluble factors derived from feeder cells. The Examiner admits that Bodnar does not teach using a human feeder cell for conditioning the media. However, the Examiner contends that Bongso teaches the development of human embryos to blastocyst stage on human tubal epithelial monolayers, and then after blastocyst formation, the hatched ICM and trophoblast were allowed to attach to the feeder monolayer. Therefore, the Examiner concludes that it would have been obvious to combine the teachings of the two references to

modify the techniques to produce conditioned medium, as taught by Bodnar, from a human cell line, as taught by Bongso, with a reasonable expectation of success. The Examiner is of the opinion that those skilled in the art would have been sufficiently motivated to make this modification, because Bongso allegedly shows that human ES cells can be grown on human feeder layers.

Applicants respectfully disagree that the claims are unpatentable in view of the combined teachings of Bodnar and Bongso.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); MPEP 2143.03. Bodnar exemplifies the growth of Rhesus monkey stem cells in medium conditioned by mouse embryo fibroblasts. Bodnar attempts to broaden the scope of his teachings by using the term "primate," however, it is indisputable that Bodnar's conditioned medium, (a) is not generated by a human fibroblast feeder, and (b) has not been shown to maintain human ES cell lines in a substantially undifferentiated state. Combining the disclosure of Bodnar with that of Bongso does not cure these deficiencies.

Bongso discloses the preparation of human ICM-derived cells in a stem cell like morphology that survive for two passages. Bongso does not teach any conditions or media for deriving or maintaining a properly characterized human ES cell line in an undifferentiated state. The Examiner has responded to this point by stating: "Applicants are arguing limitations that are not within the claims." Final Office Action, p.12, third paragraph. This is not correct, as claim 76 explicitly requires that the conditioned medium is able to support a human pluripotent embryonic stem (ES) cell line. Conditions that support merely two passages of ICM-derived cells in a stem cell like morphology, as disclosed by Bongso, would

not be considered by those skilled in the art as adequate to support a cell line. Furthermore, Bongso cultures blastocysts on human tubal epithelial monolayers. However, epithelial cells are not fibroblasts, as recited in the present claims. Therefore, the combined teachings of Bodnar and Bongso do not teach all of the limitations in the pending claims as required.

Further, the differences between the cells being cultured by Bodnar and Bongso (mouse and monkey cells in Bodnar versus human cells in Bongso), and the types of feeder cells (fibroblasts in Bodnar versus tubal epithelium in Bongso) would not provide those skilled in the art with the requisite motivation to combine the respective teachings of each other.

Moreover, Applicants respectfully submit that those skilled in the art would not have had a reasonable expectation of success in arriving at the claimed invention even when Bongso and Bodnar were combined.

Prior to the filing of the present application, there was no documented conditioned medium that was capable of maintaining hES cells and cell lines in an undifferentiated state for a prolonged period of time. Bodnar does not even show maintaining human ES cell lines in a substantially undifferentiated state. Bongso discloses the use of human feeder cells that only support two passages of human ICM-derived cells in a stem cell like morphology. In fact, even when human feeder cells were used instead of a conditioned medium in Bongso, the passaging of human ICM-derived cells did not go beyond two passages. In Bongso, the feeder layers were required to keep the cells in an undifferentiated state for only two passages. The thinking at the time was that feeders were absolutely necessary to maintain the hES cells in an undifferentiated state, and not simply to prolong the culturing. Therefore,

there would have been no expectation of success in simply replacing the human feeders with conditioned media in order to keep the human ES cells in an undifferentiated state.

In contrast, the conditioned media provided in the present invention permits prolonged culturing of cells while maintaining the cells in a proliferative, undifferentiated state. See, for example, the reference to 19th passage on page 39, line 31 of the specification. It is the ability of the conditioned media to maintain the cells of in an undifferentiated state that enables continued passaging of the cells which, in one embodiment leads to the derivation of a cell line and in another embodiment permits extended culturing of the cells of a hES cell line while maintaining the undifferentiated status and pluripotent potential of the cells. Therefore, the results achieved with the claimed conditioned media of the present invention were unexpected.

Accordingly, Applicants respectfully submit that Bodnar and Bongso, taken singularly or in combination, fail to teach the claimed condition medium. Further, the references in combination fail to provide the requisite motivation and a reasonable expectation of success in order to render the presently claimed invention obvious. Thus, the rejection under 35 U.S.C. §103(a) based on the combination of Bodnar and Bongso is overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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